SUPPORT FOR THE AMENDMENTS

Figures 3-5 and the specification has been amended.

Figures 3-5 have been amended to remove the descriptive text and to correct an inadvertent error in the Y-axis (axis of the ordinate) of Figures 4-5 where the title "Concentrations in [mg/mL]" was incorrectly presented as "Concentrations in [ng/mL]". Support for the amendments to Figures 3-5 and to the expanded description of the drawings in the specification is provided by Examples 6 and 7.

No new matter has been added by the present amendments.

REMARKS

Claims 1, 10, 12-14, 16-18, 29, 30, 32, 33, 35-38, 40, and 42-57 are pending in the present application.

The rejections of: (a) Claims 1, 10, 12-14, 16-18, 25-27, 29-30, 32-37, 43-49, and 55-57 under 35 U.S.C. §103(a) over Gefter et al (US 6,180,608) in view of Bauer et al (US 2002/039996); and (b) Claims 38, 40-42, 58 and 60 under 35 U.S.C. §103(a) over Gefter et al in view of Bauer et al and Engel et al (US 5,663,145), are respectfully traversed.

The claimed invention provides, *inter alia*, a pharmaceutical gel preparation comprising a mixture of:

(a) D-63153 or a pharmaceutically active salt thereof in lyophilized form at a concentration of from 5 to 50 mg of peptide per ml of the preparation, and

(b) an aqueous solution of sodium chloride at a concentration of from 0.05% to about 0.5% (weight/volume), and

wherein the preparation is suitable for administration after reconstitution of (a) by the mixing of (a) and (b) and after a standing time of up to about 120 minutes subsequent to the mixing of (a) and (b). (see Claim 1)

The Examiner's rejections in this case appear in paragraphs 6-10, which are substantially the same as those in paragraphs 7-11 of the Office Action mailed April 1, 2009, and appears in paragraphs 14-16, which are substantially the same as those in paragraph 15-17 of the Office Action mailed April 1, 2009. Applicants provide the following arguments against the rejections in general and toward the Examiner's responses in paragraphs 12 and 18 of the outstanding Office Action.

The present invention relates to a sustained release pharmaceutical administration form, as well as methods and kits, where the form is a pharmaceutical gel preparation

containing D-63153. As the Examiner recognizes, Gefter et al fails to disclose or suggest D-63153.

Gefter et al provides the therapeutic effectiveness of a pharmaceutically active peptide which seeks to be maintained *in vivo* over prolonged time periods to treat hormone-dependent diseases. To this end, Gefter et al disclose a pharmaceutical composition comprising a water-insoluble complex composed of a peptidic compound and a macromolecule carrier that allows for sustained release of the peptidic compound in vivo upon administration of the complex. The peptidic compound of Gefter et al comprises peptides, polypeptides and proteins. The peptidic compound can also comprise an LHRH analogue which may be an LHRH agonist or an LHRH antagonist in a narrower sense, including the exemplary the LHRH antagonists PPI-149, PPI-258 and cetrorelix.

In Gefter et al, the carrier macromolecule comprises cationic carrier macromolecule like poly-L-lysine and other polymers of basic amino acids or anionic carrier macromolecule like polyalcohol derivatives, specifically polysaccharides and more specifically carboxymethylcellulose, algin, alginate, acetate polymers, acrylic polymers, alkali starch glycolate and others.

The current invention does not comprise a carrier macromolecule and does not use such carrier macromolecule. On the contrary the inventive peptide forms the administration form for sustained release itself.

In the Office Action mailed December 21, 2009, the Examiner disregards the foregoing as being irrelevant due to the usage of the transitional phrase "comprising". Although Applicants agree that the "comprising" terminology permits the inclusion of additional components, it is noted that the form of the product is important. Indeed, in Gefter et al the carrier macromolecule is necessary to permit formation of a sustained release complex where in contrast the claimed invention the sustained release complex is formed

after reconstitution of a lyophilized form D-63153 or a pharmaceutically active salt thereof at a concentration of from 5 to 50 mg of peptide per ml of the preparation by mixing this lyophilized form with an aqueous solution of sodium chloride at a concentration of from 0.05% to about 0.5% (weight/volume). Thus, the language of the claim contemplates a distinct structure from that disclosed in Gefter et al, even putting aside the fact that Gefter et al fails to disclose D-63153.

Again, Applicants submit that Gefter et al use a 0.9% sodium chloride in Example 14 as a reconstitution vehicle to reconstitute the complex PPI-149-CMC, consisting of the peptidic compound PPI-149 and the macromolecule carboxymethylcellulose, wherein the complex PPI-149-CMC is already a sustained delivery complex. However, the present invention uses sodium chloride as an inorganic salt as the reconstitution medium and to prepare a sustained release form from an easily soluble peptide or peptide salt. In the Office Action mailed December 21, 2009, the Examiner alleges that reconstitution of PPI-149 in 0.9% NaCl disclosed by Gefter et al meets the limitation in the claims requiring reconstitution of a lyophilized form D-63153 or a pharmaceutically active salt thereof at a concentration of from 5 to 50 mg of peptide per ml of the preparation by mixing this lyophilized form with an aqueous solution of sodium chloride at a concentration of from 0.05% to about 0.5% (weight/volume). Applicants disagree.

First, it is again submitted (and apparently recognized by the Examiner) that Gefter et al does not disclose or suggest D-63153 or a pharmaceutically active salt thereof. Bauer et al does not specifically disclose this reconstitution step.

Second, as stated above, Gefter et al use a 0.9% sodium chloride in Example 14 as a reconstitution vehicle to reconstitute the complex PPI-149-CMC, consisting of the peptidic compound PPI-149 and the macromolecule carboxymethylcellulose, wherein the complex

PPI-149-CMC is *already a sustained delivery complex*. This is not what is claimed. The claims relate to reconstitution of the lyophilized form of D-63165.

Further, Gefter et al discloses differing sodium chloride concentrations (Official Action pages 7-8, numbered paragraphs 9-10). However, the Examiner alleges that Bauer et al disclose a pharmaceutical administration form containing peptides prone to aggregation in the form of their acetate, gluconate, glucuronate, lactate and others.

Bauer et al discloses that peptides have a nature prone to uncontrolled aggregation and that the peptides if administered lead to a concentration-dependent lowering of the bioavailability from the peptide concentration. Bauer at al therefore disclose that addition of a free acid to the easily soluble peptide salt prevents that peptide salts prone to aggregation. The combination of the teaching of Gefter et al and of Bauer et al does not lead to the inventive subject matter.

Moreover, as recognized by the Examiner, Bauer et al does not actually disclose or suggest D-63153. The Examiner cites paragraph [0014] of Bauer et al, which states "The peptides employed are the LHRH antagonists antide, A-75998, ganirelix and Nal-Glu antagonist, but in particular cetrorelix, antarelix, and the antagonists according to the U.S. Pat. No. 5,942,493 and DE 19911771.3." These references disclose a large number of peptides, one of which is D-63153. However, Bauer et al or these references fail to provide any specific motivation to select D-63153 for use as presently claimed.

Applicants wish to further note that the Examiner emphasizes that Bauer et al disclose a pharmaceutical administration form which contains peptides prone to aggregation. Bauer et al provide a teaching to *avoid aggregation* of the peptides whereas the presently claimed invention is a sustained release formulation and consequently involves the aggregation of peptides by reconstitution of lyophilized peptide salts with inorganic salts or acetic acid salts. Thus, the mechanism by which the claimed invention is achieved as compared to the cited are

at direct odds and are incompatible. The Examiner makes no attempt to address this deficiency Bauer et al and the incompatibility of the disclosures of Bauer et al and Gefter et al. The Examiner is reminded that "If proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification." *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984)

Applicants again submit that the teachings of Bauer et al are not relevant to the claims of the present application. It is only when Applicants disclosure is used as a guidepost to reconstitute the claimed invention with the benefit of hindsight that the disclosure of Geftner et al and Bauer et al are combinable. In all other proper circumstances, the skilled artisan would not find modification in the disclosure of Bauer et al to modify the disclosure of Geftner et al at least due to the direct contradiction in the disclosures identified above. Instead of addressing this deficiency, the Examiner resorts to boilerplate reliance upon *In re McLaughlin*. Thus, the claimed invention is not obvious in view of the combined disclosures of Geftner et al and Bauer et al.

To further illustrate the beneficial results flowing from the claimed invention, Applicants direct the Examiner's attention to the Examples of the present application. In each of Examples 1-7, D-63153 is reconstituted in a solution of sodium chloride. Indeed, Examples 1 to 7 describe numerous examples where D-63153 is reconstituted in 0.1% to 0.2% sodium chloride. In Example 2, D-63153 reconstituted in 0.1% sodium chloride is shown to retain absolute bioavailability. Example 3 illustrates the testosterone-suppressing potential of D-63153 reconstituted in 0.1% sodium chloride. Examples 4-7 provide various viscosity studies with D-63153 reconstituted in 0.1% to 0.2% sodium chloride, with Example 7 illustrating the clear advantages obtained by reconstitution of D-63153 in sodium chloride.

Geftner et al and Bauer et al do not disclose or suggest these illustrated effects and, as such, it cannot be fairly considered that such an effect would be expected.

The Examiner attempts to disregard this evidence by arguing that it "cannot be compared" since the data is only for 0.1% NaCl. The Examiner's comments rely upon the Gefter et al reconstitution in 0.9% NaCl; however, for the reasons given above, this concentration of NaCl from Gefter et al is not relevant to the claimed invention as this concentration relates to reconstitution of a complex where PPI-149-CMC is *already a sustained delivery complex*. This is not what is claimed. The claims relate to reconstitution of the lyophilized form of D-63165.

Moreover, "Evidence of unobvious or unexpected advantageous properties, such as superiority in a property the claimed compound shares with the prior art, can rebut *prima facie* obviousness. "Evidence that a compound is unexpectedly superior in one of a spectrum of common properties . . . can be enough to rebut a *prima facie* case of obviousness." No set number of examples of superiority is required. *In re Chupp*, 816 F.2d 643, 646, 2 USPQ2d 1437, 1439 (Fed. Cir. 1987)" Thus, the experimental data discussed above from the specification clearly illustrates that substantial benefits flowing from the claimed composition, which are enough to rebut even a *prima facie* case of obviousness.

In a further consideration the Examiner refers to the Engel et al, and alleges that the current invention in claims 38, 40, and 42 is obvious. Applicants disagree for the reasons already of record, coupled with the evidence provided above. For sake of completeness, Applicants reassert the following with respect to the kit claims.

Engel et al teach a kit comprising an initial dose of an LHRH antagonist and at least one maintenance dose of the same LHRH antagonist for the treatment of hormone-dependent conditions. The current invention claims in claims 38-42 and 58-60 relate a kit comprising an LHRH antagonist as finished preparation of the peptide compound and a solution of an

inorganic salt or acetic acid salt for reconstitution. In view of the foregoing, the combination of the teaching of Gefter et al, Bauer et al, and of Engel et al does not lead to the inventive subject matter of the kit claims.

The Examiner also cited Engel et al as allegedly disclosing a kit comprising an initial dose of an LHRH antagonist and at least one maintenance dose of the same LHRH antagonist for the treatment of hormone-dependent conditions. The presently claimed invention relates to kit comprising an LHRH antagonist as a finished preparation of the peptide compound and a solution of sodium chloride for reconstitution. Applicants submit that a combination of the teaching of Gefter et al, Bauer et al, and Engel et al would not directly lead a person skilled in the art to the subject matter of the aforementioned kit claims neither to any other amended claim as proposed herein for the reasons already provided above.

Applicants further submit that it is a remarkable fact that Engel et al disclose a dosage regimen of the pharmaceutical composition in which lyophilisate ampoules are in the form of an acetate and it is not intended to bring it in a slow release form according to the invention or are already in a slow release form and such slow release form is an embonate salt (and therefore in a suspended form) or the soluble peptide salt is embedded in microparticles (see column 2, lines 48-67). Such slow release form is not the starting form of the present invention.

In view of the foregoing, Applicants request withdrawal of these grounds of rejection.

The objections to Figures 3-5 is obviated by the submission of replacement Figures 3-5 and the amendment to the description thereof in the specification. Figures 3-5 have been amended to remove the descriptive text and to correct an inadvertent error in the Y-axis (axis of the ordinate) of Figures 4-5 where the title "Concentrations in [mg/mL]" was incorrectly presented as "Concentrations in [ng/mL]". Support for the amendments to Figures 3-5 and to

the expanded description of the drawings in the specification is provided by Examples 6 and 7. Thus, this ground of objection is believed to be moot.

Withdrawal of this ground of objection is requested.

Applicants respectfully submit that the above-identified application is now in condition for allowance. Early notification to this effect is earnestly solicited.

Respectfully submitted,

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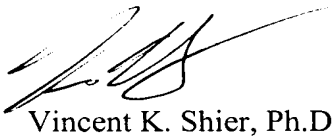

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